REMARKS

Claims 1-4, 7-12, 14, 18-22, and 24-26 are pending in the application. By the present communication, no claims have been added or canceled and claims 1-4, 11, 12, 18-22, 25, and 26 have been amended to define Applicant's invention with greater particularity. Support for the amended claim language may be found throughout the specification and claims as originally filed. Accordingly, upon entry of this amendment claims 1-4, 7-12, 14, 18-22, and 24-26 will be under consideration.

Rejections under 35 U.S.C. §112, First Paragraph

Applicant respectfully traverses the rejection of claims 1-4, 7-12, 14, 18-22, and 24-26 under on 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. (M.P.E.P. §2164.03, citing *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)).

As amended, the instant claims are directed to methods of detecting the presence of defined target nucleic acids (*e.g.*, APC, DCC, NF1, NF2, RET, VHL, or WT-1) that are present in a neoplasm and in tissue specimens that appear histologically normal upon examination. These methods provide the advantage of detecting tumor cells in tissues that appear histologically normal upon examination *before* such cells are able to grow into a tumor that is visible by standard histologic methods. Thus, such methods can be used as "an adjunct to

cytopathology" (specification at p. 4, lines 18-20) and allow the detection of tumor cells in sites external to the primary tumor, which might otherwise go undetected.

As discussed previously, the specification provides abundant guidance for the practice of the claimed methods as well as a detailed working example. Thus, based on this disclosure, one of skill in the art would have reasonably expected that mutations in any of the other recited tumor suppressor genes, which are found in the primary tumor, could similarly be detected in normal-appearing tissues into which tumor cells from the primary tumor had migrated. Accordingly, in order to practice the claimed method, the skilled artisan would simply need determine the presence of one or more of the target nucleic acids in the neoplasm and in the tissue specimen. As stated in the specification at, for example Table 1, and as is known in the art, tumor suppressor genes (*e.g.,* APC, DCC, NF1, NF2, RET, VHL, and WT-1) and mutated forms thereof have been associated with specific cancer types. Armed with this knowledge, the skilled artisan can readily assay the neoplasm and a tissue specimen that appears histologically normal upon examination for the target nucleotide sequence of the relevant tumor suppressor gene using the methods exemplified for p53.

The Office Action alleges that

> neither the specification nor the prior art provide any actual evidence that any of the genes encompassed by the instant claims had been or could be successfully detected in "histologically normal" samples at the time the instant invention was made (which is the date relevant to enablement of a claimed invention). The examiner has not disputed the fact that one could have successfully attempted such diagnostic techniques on histologically normal tissues using techniques known in the art and taught in the specification; however, enablement of the instant claims requires actual detection, not attempted detection. (Office Action, page 7).

Applicant respectfully submits that an applicant need not have actually reduced the invention to practice prior to filing. *In Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured

a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). Applicant submits that the methods of the claimed invention are directed to detection of nucleic acids, which can be used as diagnostics. As stated in the Office Action, "the examiner has not disputed the fact that one could have successfully attempted such diagnostic techniques on histologically normal tissues using techniques known in the art and taught in the specification." (Office Action, page 7). Accordingly, Applicant submits that detection of the target nucleic acids in tissues that appear histologically normal upon examination is indicative of the presence of tumor cells in such tissues.

In summary, it is submitted that one skilled in the art, in view of the present specification and that which was known in the art, would reasonably have predicted that the disclosed methods could be applied to the detection of any of the recited tumor suppressor genes, for detection in the primary tumor and in tissues that appear histologically normal upon examination. As such, Applicant submits that the skilled artisan would have known how to practice the claimed methods without undue experimentation. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge the total mount of $940.00 as payment for the Petition for One-Month Extension of Time fee ($130.00) and the Request for Continued Examination fee ($810.00) to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-referenced Attorney docket number.

Respectfully submitted,

Date: November 25, 2008

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213